Systematic Review and Meta-Analysis

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Prognostic and clinical significance of metastasis-associated gene 1 overexpression in solid cancers

A meta-analysis

Ke Ma, PhD[a,*], Yangwei Fan, PhD[b], Yuan Hu, MD[b]

Abstract

Background: In the past 2 decades, metastasis-associated gene 1 (MTA1) has attracted attention for its close association with cancer progression and its roles in chromatin remodeling processes, making it a central gene in cancer. The present meta-analysis was performed to assess MTA1 expression in solid tumors.

Materials and methods: This analysis identified studies that evaluated the relationship between MTA1 expression and clinical characteristics or prognosis of patients with solid tumors via the PubMed, Cochrane Library, and Embase electronic databases. Fixed-effect and random-effect meta-analytical techniques were used to correlate MTA1 expression with outcome measures. The outcome variables are shown as odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI).

Results: Analysis of 40 cohort studies involving 4564 cancer patients revealed a significant association of MTA1 overexpression with tumor patient age (>50 vs. <50 years: combined OR 0.73, 95% CI 0.57–0.94), tumor grade (G3/4 vs. G1/2: combined OR 1.94, 95% CI 1.48–2.53), tumor size (>3 cm vs. <3 cm: combined OR 2.35, 95% CI 1.73–3.19), T stage (T3/4 vs. T1/2: combined OR 2.11, 95% CI 1.74–2.56), lymph node metastasis (yes vs. no: combined OR 2.92, 95% CI 2.26–3.75), distant metastasis (yes vs. no: combined OR 2.26, 95% CI 1.42–3.59), TNM stage (III/IV vs. I/II: combined OR 2.50, 95% CI 1.84–3.38), vascular invasion (yes vs. no: combined OR 2.26, 95% CI 1.92–3.56), and poor overall survival time (HR 1.83; 95% CI: 1.53–2.20; $P = .000$).

Conclusions: Our analyses demonstrate that MTA1 was an effective predictor of a worse prognosis in tumor patients. Moreover, MTA1 may play important role in tumor progression and outcome, and targeting MTA1 may be a new strategy for anti-cancer therapy.

Abbreviations: CI = confidence intervals, CRC = colorectal cancer, EGFR = endothelial growth factor receptor, EMT = epithelial to mesenchymal transition, ESCC = esophageal squamous cell cancer, HCC = hepatocellular carcinoma, HDAC1/2 = histone deacetylases 1/2, HR = hazard ratio, IHC = immunohistochemistry, MTA = metastasis-associated gene 1, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, NSCLC = non-small cell lung cancer, NuRD = nucleosome remodeling and deacetylase, OR = odds ratio, OS = overall survival, VEGF = vascular endothelial growth factor.

Keywords: cancer, meta-analysis, metastasis-associated gene 1, MTA1, prognosis

1. Introduction

Tumor invasion and metastasis are unsolved challenges in the treatment of malignant tumors. Metastasis-associated protein 1 (MTA1), an essential component of the nucleosome remodeling and deacetylase (NuRD) complex, is highly associated with tumor development and metastasis.[1–3] Human MTA1 cDNA was firstly cloned by Toh to characterize the role of MTA1 in tumor genesis.[4] A large number of subsequent studies have shown that MTA1 plays pivotal roles in many malignant properties of cancers, such as therapeutic resistance,[5–7] angiogenesis,[8–11] and metastasis.[12,13] Kumar and Wang[1] used the cBioPortal genomic database to analyze the status of copy number variation in MTA1 and other members of the MTA family in human cancer, showing that MTA1 is often upregulated in human cancer and well correlated with aggressive phenotypes and, ultimately, unfavorable survival of cancer patients. MTA1 overexpression has gradually been considered a potential predictive factor for poor prognosis, although this remains slightly controversial.[14,15] Thus, with the aim to better understand the roles of MTA1 in oncology and to lay the foundation for further exploration, we performed an updated meta-analysis to explore the relationship of MTA1 expression and clinicopathological features and survival in solid carcinomas.

Compared with the previously published meta-analysis,[16] newer studies were included in the present analysis; furthermore, we also performed subgroup analysis to more precisely evaluate the relationships of MTA1 expression (both protein and gene) with clinicopathological characteristics and outcome in all reported solid cancers. Therefore, our updated meta-analysis expands the sample size and adds the newest studies on the clinical significance of MTA1, and thus contributes to a comprehensive understanding

Editor: Jianxun Ding.

KM and YF contributed equally to this work.

The authors report no conflicts of interest.

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Medicine (2018) 97:41(e12292)

Received: 7 January 2018 / Accepted: 16 August 2018

http://dx.doi.org/10.1097/MD.0000000000012292

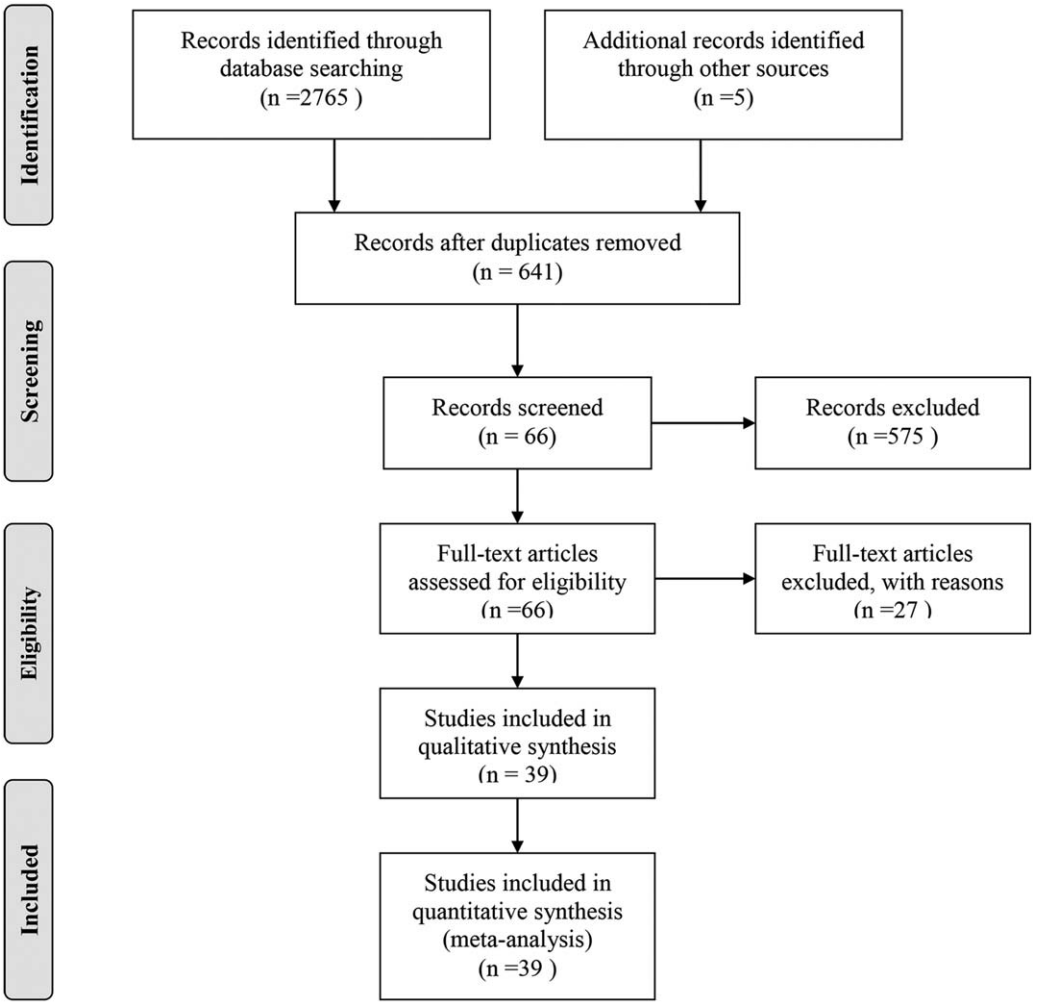

Figure 1. Flow diagram of the study selection for this meta-analysis.

of MTA1 expression and provides more accurate information for clinical application and basic research.

2. Methods

2.1. Ethics and dissemination

Ethical approval and informed consent are not required, as the study will be a literature review and will not involve direct contact with patients or alterations to patient care.

2.2. Search strategy

We performed a search of articles published in PubMed and EMBASE from January 1, 1994, through December 20, 2017. The search strategy was based on combinations of the following terms: metastasis-associated protein 1/metastasis-associated gene 1/MTA1/MTA-1 and survival/prognosis/prognostic and clinicopathological features/clinicopathological characters/clinical significance/clinical characters/clinical features.

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: articles published in the English language, evaluation of a link between MTA1 expression and clinical characteristics or prognosis of patients with any type of cancer, patients grouped according to positive or negative MTA1 expression, description of related clinicopathological parameters or overall survival (OS), studies containing sufficient data for the computation of odds ratios (OR) or hazard ratio (HR) and corresponding 95% confidence interval (CI), and sample size >30.

The exclusion criteria were as follows: nonhuman research, letters, editorials, expert opinions, case reports, and reviews; studies without usable data; duplicate publications; and articles that had been retracted.

2.4. Data extraction and quality assessment

All data extraction was performed separately by 2 independent investigators and disagreements were resolved by joint discussion. The following data were recorded for each eligible study: family name of the first author, publication year, country of origin, sample size, tumor type, detection method, cutoff values for MTA1-positive expression, number of MTA1-positive/negative patients, HR estimation with 95% CI, and clinicopathological parameters. If not directly provided in the original article, the HRs were either calculated using the method reported by Parmar et al[17] or extracted from the survival curve as

Table 1

Main characteristics and results of the included studies.

Study	Year	Country	No. of patients	Tumor type	Method	MTA1 Pos./Neg.	HR (95% CI)	NOS scores
Ma et al[24]	2017	China	56	NSCLC	IHC	41/15	1.82 (0.717–4.618)	9
Honjo et al[40]	2017	Japan	142	ESCC	IHC	82/60	1.41 (0.81–2.43)	8
Liu et al[41]	2017	China	107	ESCC	IHC	54/53	NR	8
Pavlidis et al[56]	2017	Greece	51	PC	IHC	48/3	NR	8
Li et al[25]	2016	China	125	NSCLC	IHC	49/76	1.321 (0.773–2.256)	9
Yang et al[42]	2016	China	197	ESCC	IHC	83/114	0.847 (0.578–1.241)	8
Zhou et al[29]	2015	China	118	LC	IHC	65/53	4.96 (2.40–10.25)	8
Meng et al[48]	2015	China	160	GC	IHC	70/90	NR	8
Andishehtadbir et al[39]	2014	Iran	44	OSCC	IHC	23/21	NR	7
Yuan et al[34]	2014	China	136	NPC	IHC	NR	1.006 (0.726–1.362)	8
Wang et al[58]	2014	China	108	GA	IHC	33/34	3.06 (1.37–6.87)	8
Lin et al[35]	2014	China	60	NPC	IHC	29/31	NR	6
Deng et al[9]	2013	China	111	GC	IHC	40/71	3.69 (1.771–7.668)	6
Liu et al[59]	2013	China	132	CC	IHC	73/59	3.486 (1.274–9.537)	8
Song et al[43]	2013	China	174	ESCC	IHC	79/95	1.758 (1.194–2.587)	7
Jin et al[52]	2012	Korea	303	HCC	IHC	104/199	1.848 (0.929–3.676)	7
Li et al[36]	2012	China	208	NPC	IHC	101/107	1.98 (1.09–3.59)	9
Li et al[44]	2012	China	131	ESCC	IHC	57/74	1.30 (0.806–2.096)	8
Prisco et al[60]	2012	Italy	81	OC	IHC	NR	2.0 (0.9–4.3)	6
Cheng et al[30]	2012	Taiwan	150	BC	PCR	60/90	1.78 (0.8–3.94)*	6
Deng et al[37]	2012	China	60	NPC	ISH	43/17	1.843 (1.068–3.179)	8
Mao et al[31]	2012	China	102	BC	IHC	30/72	NR	6
Yu et al[26]	2011	China	60	NSCLC	IHC	22/38	5.226 (1.575–17.338)	8
Li et al[10]	2011	China	102	NSCLC	IHC	41/61	2.17 (1.105–4.247)	9
Higashijima et al[50]	2011	Japan	74	Colon Cancer	IHC	38/36	1.86 (1.00–3.46)	6
Park et al[38]	2011	Korea	43	TC	IHC	18/25	2.44 (0.64–9.3)*	8
Xu et al[27]	2011	China	96	NSCLC	IHC	61/35	NR	7
Sharma et al[32]	2011	India	89	BC	IHC	50/39	NR	7
Du et al[51]	2011	China	81	CRC	IHC	25/56	NR	8
Zhu et al[28]	2010	China	100	NSCLC	IHC	67/33	2.452 (1.324–4.543)	8
Li et al[45]	2009	China	90	ESCC	IHC	40/50	2.708 (1.475–4.971)	8
Ryu et al[53]	2008	Korea	506	HCC	IHC	88/418	1.91 (1.35–2.71)	7
Miyake et al[57]	2008	Japan	39	PC	IHC	13/26	0.84 (0.44–1.49)*	6
Jang et al[33]	2006	Korea	263	BC	IHC	67/196	1.26 (0.63–2.54)	7
Toh et al[46]	2004	Japan	70	ESCC	IHC	30/40	2.95 (1.44–6.02)	9
Moon et al[54]	2004	Korea	45	HCC	IHC	31/14	NR	7
Hamatsu et al[55]	2003	Japan	33	HCC	PCR	14/19	NR	7
Toh et al[47]	1999	Japan	47	ESCC	PCR	16/31	NR	6
Toh et al[49]	1997	Japan	36	CRC	PCR	14/22	NR	6
Toh et al[49]	1997	Japan	34	GC	PCR	13/21	NR	6

BC = breast cancers, CC = cervical cancer, CI = confidence interval, CRC = colorectal cancer, ESCC = esophageal squamous cell cancer, GA = gallbladder adenocarcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, IHC = immunohistochemistry, ISH = in situ hybridization, LC = lung cancer, MTA = metastasis-associated gene, Neg. = negative, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, NR = data were not reported, NSCLC = non–small cell lung cancer, OC = ovarian carcinoma, OSCC = oral squamous cell carcinomas, PC = pancreatic carcinoma, Pos = positive , TC = tonsil cancer.

* Extrapolated from survival curve.

Table 2

The relationship between MTA1 expression and clinicopathological characters in solid tumor patients.

Parameter	No. of study (no. of patients)	MTA1 positive (no. of patients)	OR (95% CI, *P*)	I^2 (*P*)	H-M
Sex					
Female vs. male	30 (985 vs. 2493)	412 vs. 976	1.00 (0.85–1.18, .98)	2% (.43)	Fixed
Age, y					
>60 vs. <60	8 (437 vs. 342)	196 vs. 167	0.86 (0.64–1.16, .32)	9% (.36)	Fixed
>50 vs. <50	9 (743 vs. 561)	308 vs. 250	0.73 (0.57–0.94, .01)	0% (.78)	Fixed
>45 vs. <45	3 (153 vs. 189)	74 vs. 83	0.92 (0.56–1.52, 75)	8% (.34)	Fixed
Tumor differentiation					
Poor vs. well/moderate	18 (484 vs.1174)	242 vs. 506	1.37 (0.98–1.91, .06)	48% (.01)	Random
Tumor grade					
G3/4 vs. G1/2	9 (713 vs. 892)	219 vs. 267	1.94 (1.48–2.53, .00001)	35% (.13)	Fixed
Tumor size					
>3 cm vs. <3cm	9 (739 vs. 351)	372 vs. 114	2.35 (1.73–3.19, <.00001)	0% (.46)	Fixed
>5 cm vs. <5cm	9 (413 vs. 862)	190 vs. 359	1.45 (0.87–2.42, .16)	75% (.0001)	Random
Tumor T stage					
T3/4 vs. T1/2	23 (1029 vs. 1232)	570 vs. 547	2.11 (1.74–2.56, <.00001)	0% (.83)	Fixed
Lymph node metastasis					
Yes vs. no	23 (1111 vs. 1197)	622 vs. 403	2.92 (2.26–3.75, <.00001)	43% (.02)	Random
Distant metastasis					
Yes vs. no	5 (107 vs. 374)	69 vs. 179	2.26 (1.42–3.59, .0005)	0% (.63)	Fixed
Tumor TNM stage					
III/IV vs. I/II	18 (919 vs. 1061)	501 vs. 405	2.50 (1.84–3.38, <.00001)	49% (.01)	Random
Vascular invasion					
Yes vs. no	10 (391 vs. 855)	184 vs. 186	2.62 (1.92–3.56, <.00001)	0% (.67)	Fixed

CI = confidence interval, Fixed = fixed-effect model, H-M = Heterogeneity model, MTA = metastasis-associated gene 1, OR = odds ratio, Random = random-effect model.

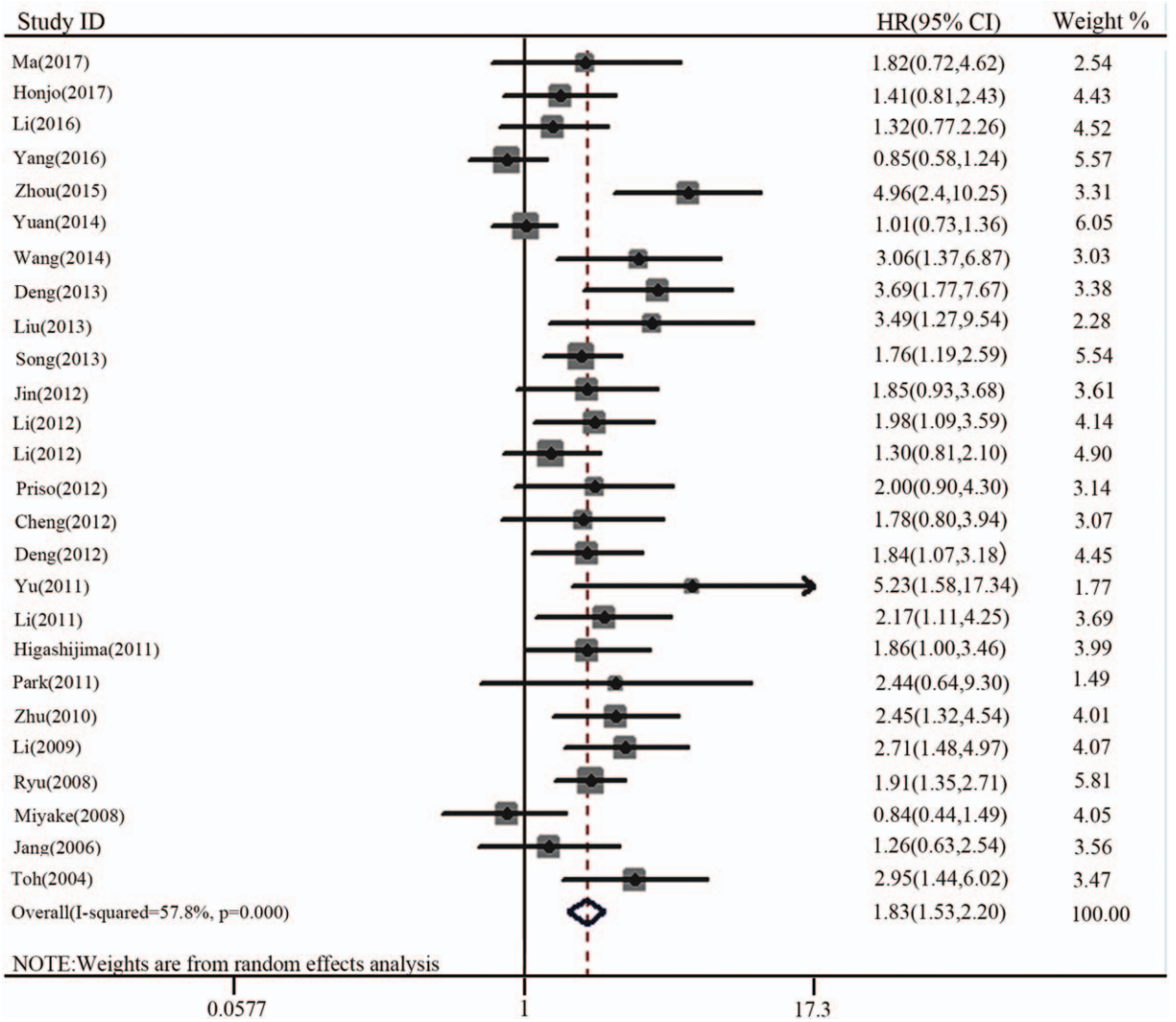

Figure 2. Forest plot of the pooled HR for MTA1 expression in carcinomas. CI = confidence interval, HR = hazard ratio.

described by Tierney et al.[18] Eligible studies were assessed according to the Newcastle-Ottawa Scale[19] by 2 authors separately. The studies included in the present meta-analysis were identified as having high-quality methodology with at least 6 scores.

3. Statistical analyses

Stata 12.0 software (STATA Corporation p, College Station, TX) and Review Manager 5.3 software (Cochrane Collaboration, London, UK) were employed as a statistical platform for the pooled analysis. Combined HRs and 95% CIs were used to assess the strength of association of MTA1 expression with OS. The statistical significance of the pooled HRs was determined by a Z test. $P < .05$ indicated statistical significance. Heterogeneity was assessed using I^2 and Q statistics.[20] If heterogeneity was observed ($I^2 > 50\%$ or $P < .10$), a random-effect model (Der Simonian and Laird method) was used for analysis. In other cases, a fixed-effect model (Mantel-Haenszel method) was adopted.[21] Egger linear regression test, Begg funnel plot test, and the trim-and-fill method were used to evaluate publication bias.[22,23] Sensitivity analysis was conducted by removing each study and recalculating the combined HR. All statistical tests were 2-sided, and the significance level was set at 0.05.

4. Results

4.1. Characteristics of the included trials

The flow chart of the literature search is shown in Figure 1. After screening the abstracts and full-texts, a total of 40 studies (39 literatures) involving 4564 cancer patients were included in the meta-analysis; the main characteristics of the 40 studies are summarized in Table 1. All 40 retrospective cohort studies were published between 1997 and 2017. Among the included studies, 7 were of lung cancer (non-small cell lung cancer [NSCLC]: 6 cases,[10,24–28] lung cancer: 1 case[29]), 4 studies were of breast cancer,[30–33] 6 were of head and neck cancer (nasopharyngeal carcinoma [NPC]: 4 cases,[34–37] tonsil cancer: 1 case,[38] oral squamous cell carcinomas: 1 case[39]), 20 of digestive tract cancers (esophageal squamous cell cancer [ESCC]: 8 cases,[40–47] gastric cancer: 3 cases,[9,48,49] colon cancer: 1 case,[50] colorectal

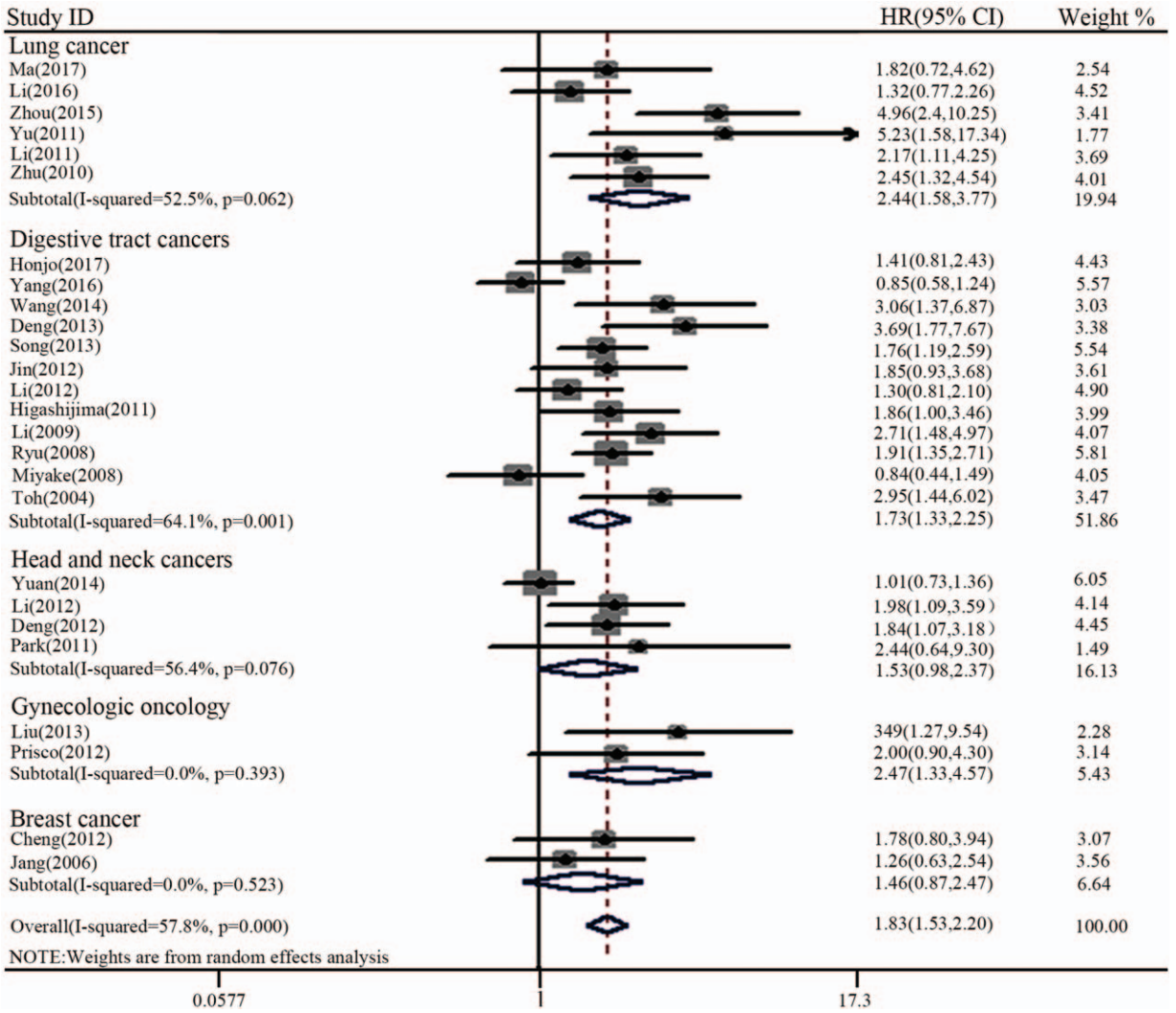

Figure 3. Forest plot depiction of MTA1 expression and HR according to tumor type. CI = confidence interval, HR = hazard ratio.

cancer [CRC]: 2 cases,[49,51] hepatocellular carcinoma [HCC]: 4 cases,[52–55] pancreatic carcinoma: 2 cases,[56,57] gallbladder adenocarcinoma: 1 case[58]), and 2 of gynecologic cancers (cervical cancer: 1 case,[59] ovarian carcinoma: 1 case[60]).

Twenty-two studies evaluated patients from China, 5 from Korea, 8 from Japan, 1 from Taiwan, 1 from Italy, 1 from Iran, 1 from India, and 1 from Greece.

4.2. The association between MTA1 expression and clinical features

To understand the role of MTA1 expression in tumor progression, we examined the relationship between MTA1 expression and clinicopathological characters in solid tumor patients. As shown in Table 2, MTA1 expression was significantly associated with age (>50 vs. <50 years: combined OR 0.73, 95% CI 0.57–0.94), tumor grade (G3/4 vs. G1/2: combined OR 1.94, 95% CI 1.48–2.53), tumor size (>3 cm vs. <3 cm: combined OR 2.35, 95% CI 1.73–3.19), T stage (T3/4 vs. T1/2: combined OR 2.11, 95% CI 1.74–2.56), lymph node metastasis (yes vs. no: combined OR 2.92, 95% CI 2.26–3.75), distant metastasis (yes vs. no: combined OR 2.26, 95% CI 1.42–3.59), TNM stage (III/IV vs. I/II: combined OR 2.50, 95% CI 1.84–3.38), and vascular invasion (yes vs. no: combined OR 2.26, 95% CI 1.92–3.56). However, MTA1 overexpression was not significantly associated with tumor differentiation (poor vs. well/moderate, $P = .06$), tumor size (>5 cm vs. <5 cm, $P = .16$, sex (female vs. male, $P = .98$), and age (>60 vs. <60 or >45 vs. <45 years, $P = .32$ and .75, respectively).

4.3. The association between MTA1 expression and OS

The above results indicated that MTA1 plays accelerating roles in tumor development; thus, we next analyzed whether MTA1 expression contributes to the poorer prognosis of carcinoma patients. The results of our random-effects network meta-analysis for OS are summarized in Figure 2. Twenty-six studies presenting data on MTA1 expression and OS in 3579 cancer patients showed an associated between elevated MTA1 expression and a shorter OS, with a pooled HR of 1.83 (95% CI: 1.53–2.20; $0 = .000$). However, owing to significant between-study heterogeneity ($I^2 = 57.8\%$, $P = .000$), we performed further

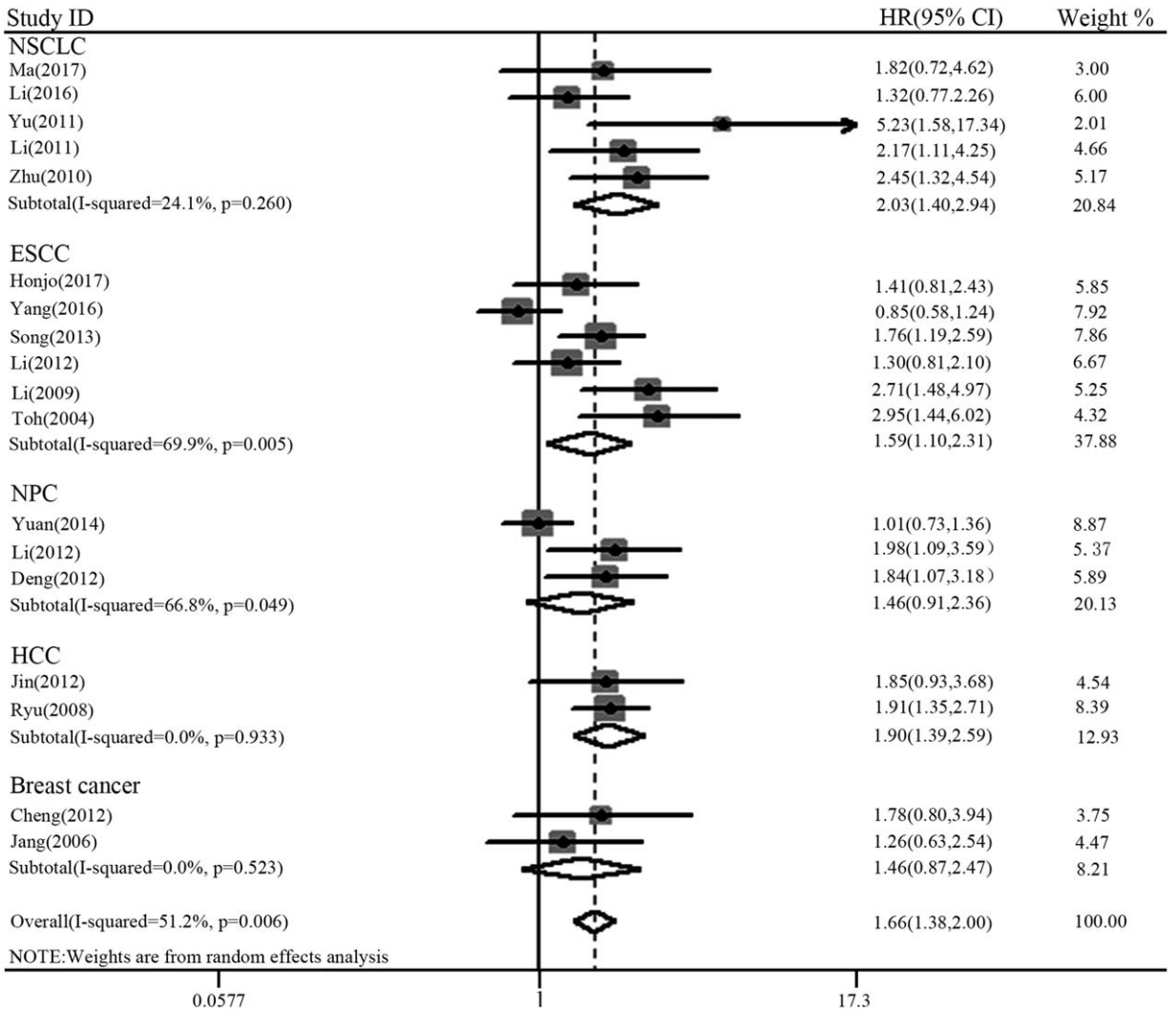

Figure 4. Forest plot depiction of MTA1 expression and HR according to single tumor types with >2 cases. CI = confidence interval, HR = hazard ratio.

subgroup analyses according to tumor type, country, cut-offs, analysis method, and examination method to evaluate the effect of MTA1 on OS.

Based on tumor type, we observed poor survival time with MTA1 overexpression in lung cancer (n = 6, HR 2.44, 95% CI: 1.58–3.77; *P* = .000), digestive tract cancers (n = 12, HR 1.73, 95% CI: 1.33–2.25; P = .000), and gynecologic oncology (n = 2, HR 2.47, 95% CI: 1.33–4.57; P = .000) (Fig. 3). However, MTA1 overexpression was not a significant prognostic factor in breast cancer (n = 2, *P* = .155) or head and neck cancer (n = 4, *P* = .060) (Fig. 3). Additionally, considering tumor heterogeneity, we performed further stratification analysis on single tumor with >2 cases. In accordance with the subgroup analysis according to tumor type, high expression of MTA1 indicated a poor prognosis in NSCLC (n = 5, HR 2.03, 95% CI: 1.40–2.94; *P* = .000), ESCC (n = 6, HR 1.59, 95% CI: 1.10–2.31; *P* = .014), and HCC (n = 2, HR 1.90, 95% CI: 1.39–2.59; *P* = .000), but not in NPC (n = 3, P = 0.118) or breast cancer (n = 2, *P* = .155) (Fig. 4).

Univariate (n = 6, HR 1.84, 95% CI: 1.23–2.74; *P* = .003) and multivariate analysis (n = 20, HR 1.84, 95% CI: 1.49–2.27; *P* = .000) (Fig. 5) showed that MTA1 expression was not only associated with OS but also an independent prognostic factor. Further subgroup analysis according to patient source, cutoff, and MTA1 expression detection method is shown in Table 3.

4.4. Sensitivity analysis

Sensitivity analysis was performed to assess the effect of a single study on the overall meta-analysis results by omitting 1 study at a time from the total population. The results indicated that no point estimate of the omitted individual study lays outside the 95% CI of the combined analysis based on the overall HR estimate (Fig. 6), indicating that no individual study dominated the meta-analysis results.

4.5. Publication bias

Begg funnel plots and Egger tests were used to assess publication bias in the meta-analysis. In the OS group, the Begg test did not display obvious publication bias for the HR evaluations of OS (Begg test, Pr > Z = 0.074) (Fig. 7A). However, Egger test results

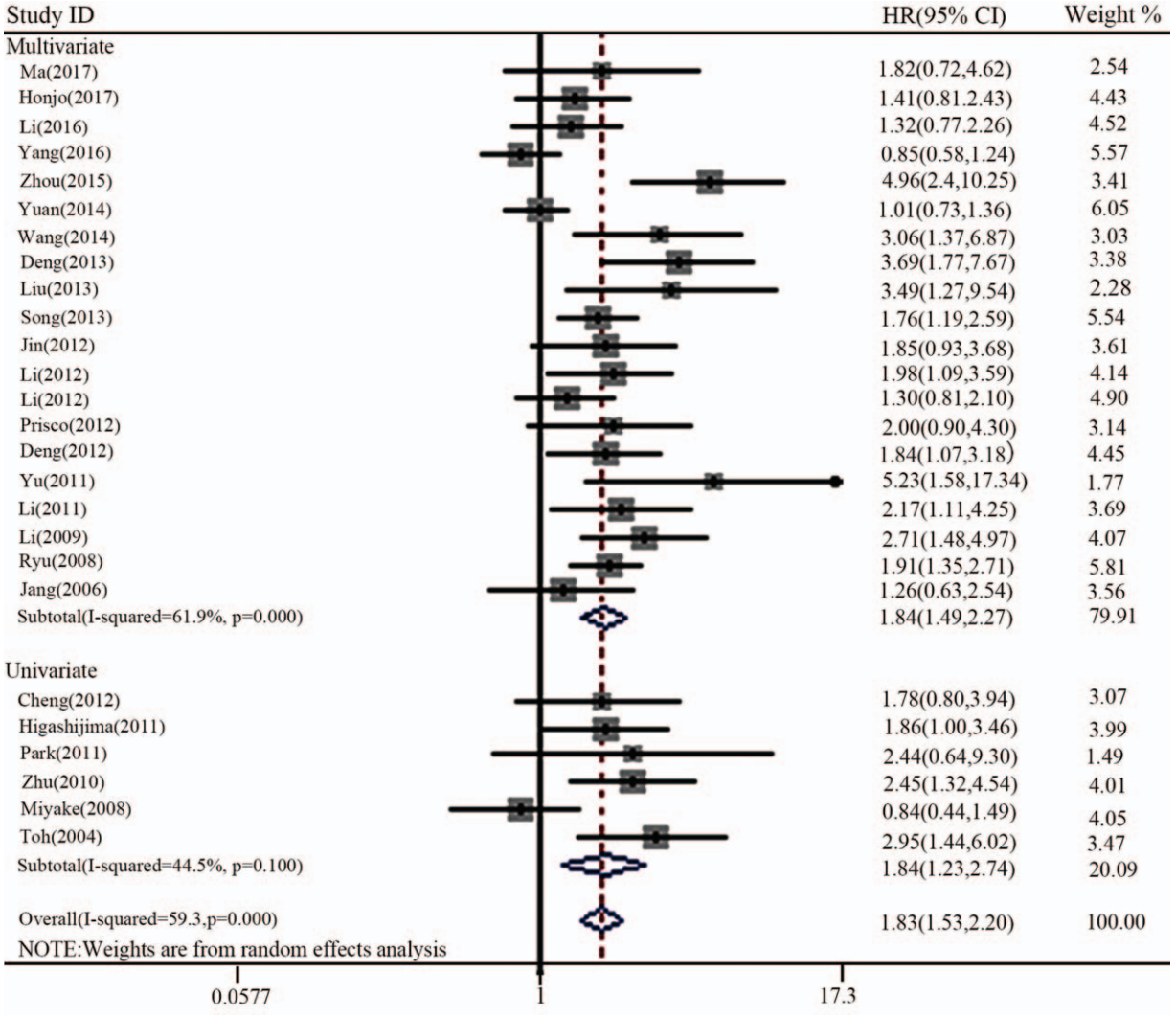

Figure 5. Forest plot depiction of MTA1 expression and HR according to the method used to perform the survival analysis. CI = confidence interval, HR = hazard ratio.

Table 3

Subgroup analysis of MTA1 expression and HR in tumor patients.

Parameter	I^2 (*P*)	HR (95% CI; *P*)
Country		
China	67.8% (.000)	1.96 (1.52–2.52; .000)
Korea	0.0% (.724)	1.797 (1.361–2.373; .000)
Japan	59.5% (.060)	1.56 (0.96–2.54; .074)
Italy	NR	2.00 (0.91–4.37; .082)
MTA1 expression		
Protein	61.1% (.000)	1.84 (1.51–2.24; .000)
Gene	0.0% (.944)	1.82 (1.16–2.86; .009)
MTA1 cutoff		
Scores ≥2	71.7% (.007)	1.96 (1.12–2.45; .019)
Scores ≥4	0.0% (.567)	1.69 (1.37–2.10; .000)
Scores >4	53.4% (.147)	3.39 (1.71–6.76; .001)
>10%	55.5% (.134)	2.73 (1.03–7.26; .044)
Other	57.1% (.013)	1.54 (1.18–2.02; .002)

CI = confidence intervals, HR = hazard ratio, nMTA = metastasis-associated gene 1, NR = only 1 study included in the group and the I^2 cannot be calculated.

showed a significant publication bias (Fig. 7B, $P = .000$). Therefore, we used the trim-and-fill method to further evaluate the publication bias. As shown in Figure 7C, after filling the meta-analysis to 39 studies, the pooled HR was 2.855 (95% CI 2.456–3.319, $P = .000$), indicating that although there was a publication bias, the results were relatively stable and credible.

5. Discussion

Physiologically, MTA1 plays critical roles in liver cell proliferation and differentiation,[61] embryonic development,[62] inflammation, and immunity regulation.[14,63,64] Pathologically, the role of MTA1 in tumor occurrence and progression has attracted attention. In addition to metastasis, MTA1 also contributes to angiogenesis, cell proliferation, and therapeutic resistance.[2,64] Nagaraj et al[65] reported that MTA1 is a proangiogenesis protein and could promote vascular endothelial growth factor (VEGF)-induced angiogenesis.[60] Additionally, MTA1 can regulate the expression of many signaling factors, such as endothelial growth

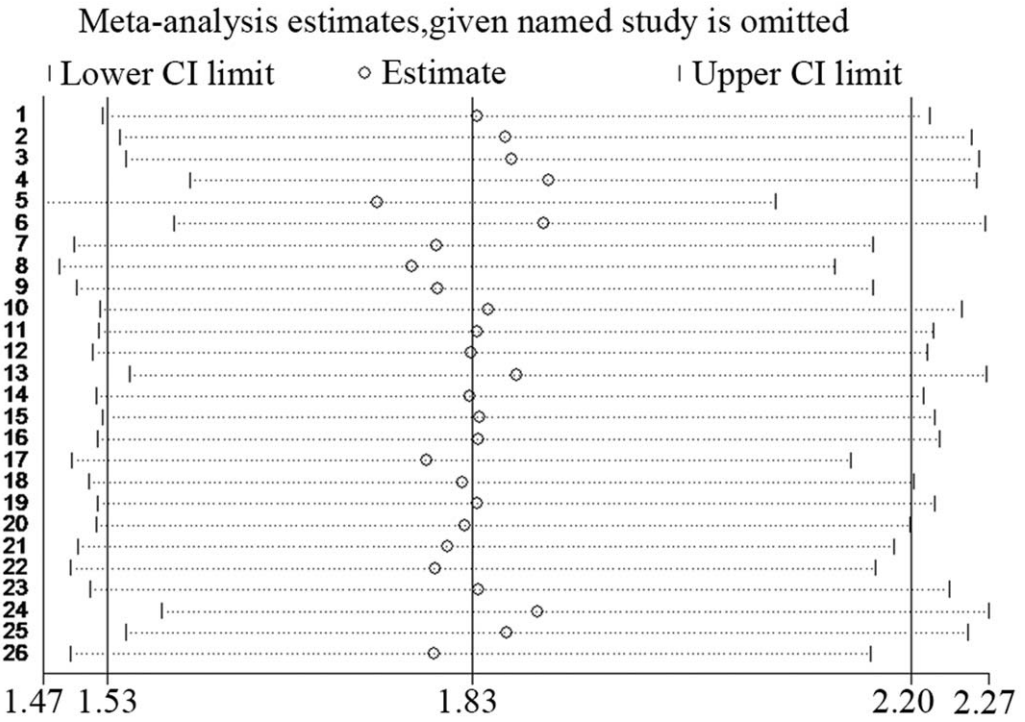

Figure 6. Sensitivity analysis of the summary HR coefficients of the relationships between MTA1 expression and overall survival. CI = confidence interval, HR = hazard ratio.

factor receptor, KRAS, and VEGF, by forming complexes with RNA polymerase II, to indirectly participate in epithelial to mesenchymal transition (EMT).[60,61] EMT is a key step in invasion and metastasis of human cancers.[66] Furthermore, MTA1 contributes to tumor metastasis by inducing EMT in some cancers.[24,67–71]

Not surprisingly, in the present updated analysis, from a total of 40 studies involving 4564 cancer patients, MTA1 expression was correlated with tumor grade, lymph node metastasis, distant metastasis, TNM stage, and vascular invasion, which were consistent with the function of MTA1 overexpression in promoting metastasis reported in the above-mentioned studies. Therefore, we can conclude that the results of these fundamental studies provide the theological basis, whereas the results of the present meta-analysis further confirm the clinical significance of the metastasis-associated protein MTA1, indicating that it may be a target to anti-tumor metastasis. However, in a comprehensive analysis of the MTA1 gene in neoplastic tissue, Hofer et al[72] showed that MTA1 is ubiquitously expressed in benign and malignant tumors and that MTA1 expression is associated with tissue invasion but may not be sufficient for progression to metastatic stages.

Taking a further step, we analyzed the correlation between MTA1 expression and OS of tumor patients. In accordance with the previous meta-analysis by Luo et al,[16] we also found that MTA1 overexpression is a poor prognostic factor of tumor patients. In subgroup analysis, higher MTA1 expression with a significantly poorer prognosis was observed in lung cancer, digestive tract cancers, and gynecologic oncology. Coincidentally, Cao et al[73] also found that MTA1 expression is related to 1-, 3-, and 5-year OS of patients with digestive tract cancers. The results suggest that MTA1 expression in lung cancer, digestive tract cancers, and gynecologic oncology may be an indicator of the prognosis. However, Sheridan et al[74] reported that only MTA1 protein levels but not DNA or mRNA alteration predicted recurrence in prostate cancer, whereas Luo et al's[16] meta-analysis only incorporated studies in which the MTA1 expression was detected by immunohistochemistry. Our subgroup analysis showed that both MTA1 protein and gene expression affected the prognosis of tumor patients. The difference may be caused by the limited number of studies of MTA1 gene expression.

6. Limitations

Our updated meta-analysis included the most recently punished studies and excluded articles published in Chinese. We also included studies that analyzed MTA1 expression in various tumors. Thus, our meta-analysis provided a more comprehensive understand of MTA1 expression in malignant tumors, which not only contributes to the cancer progression and metastasis but also predicts the prognosis of tumor patients. However, the present mate-analysis has several limitations. First, the meta-analysis was based on retrospective data and the level of evidence was lower than that obtained by randomized controlled trials. Second, because of different types of cancers, the techniques used to detect MTA1 expression and the cutoff values were different in each eligible study. Third, almost all patients included in this present meta-analysis were Asian. Because of this, our results may only be generalizable to patients from Asia. Fourth, many of the included studies reported positive results because negative results may be less likely to be published.

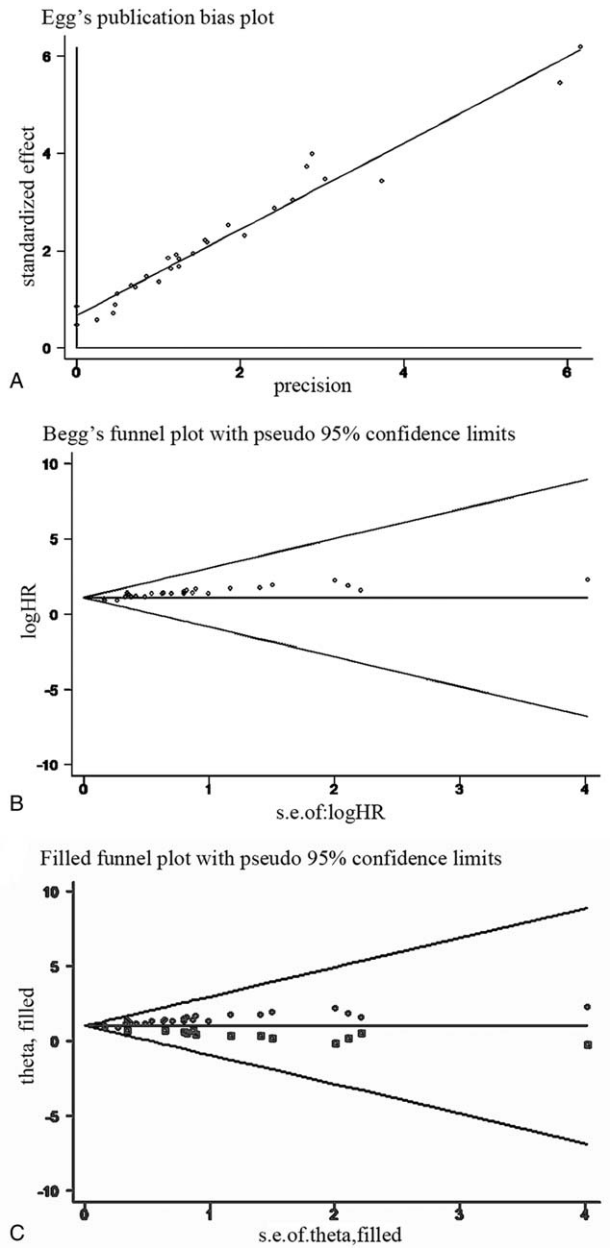

Figure 7. Publication bias plot for assessment of potential publication bias in the included studies. (A) Begg funnel plot; (B) Egger funnel plot; (C) Filled funnel plot.

6.1. Conclusions and perspectives

Despite these limits, our meta-analysis presents evidence that MTA1 overexpression is associated with tumor grade, lymph node metastasis, distant metastasis, TNM stage and vascular invasion, and OS of tumor patients. Therefore, MTA1 contributes to the progression and poor OS of malignant carcinomas and may be a promising therapeutic target. Regrettably, at present, there is no information regarding drugs, which could directly affect MTA1. However, as MTA1 is part of the NuRD complex, which also contains histone deacetylases 1 and 2 (HDAC1 and HDAC2),[1–3] and also forms the MTA1/HDAC complex with HDAC, an important regulator of MTA1,[8,75,76] one approach is to target HDACs. A number of small molecule drugs targeting HDACs have been developed and used alone or in combination with other drugs in the clinic,[77] but have mostly achieved favorable results in hematological malignancies. The present meta-analysis revealed that HDAC inhibitors may be promising agents for treating anti-solid tumors, especially in lung cancer and digestive tract cancers, which requires further in-depth investigation. In addition, small peptides or compounds that target the HDAC1/MTA1 complex have also been designed and developed[78,79] and shown to have effective anti-invasion and metastasis abilities in in-vivo animal models and in-vitro cell-based assays. Therefore, MTA1 may be a promising therapeutic target, and examination of MTA1 expression in solid tumors may be a good method to indicate prognosis.

Author contributions

Conceptualization: Ke Ma.
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Investigation: Yuan Hu.
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Acknowledgment

The authors sincerely thank the Editage for helping us edit our manuscript professionally.

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